CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74415

Trade Name Sucralfate Tablets USP 1g

Generic Name Sucralfate Tablets USP 1g

Sponsor Martec Pharmaceutical, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74415

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)				
Chemistry Review(s)	X			
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Pharmacology Review(s)				
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Bioequivalence Review(s)	X			
Administrative Document(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74415

APPROVAL LETTER

HFD-205

ANDA 74-415

JUN 8

Martec Pharmaceutical, Inc.
Attention: Paul T. Sudhakar
U.S. Agent for: ratiopharm GmbH & Co. Arzneimittel
1800 North Topping
P.O. Box 33510
Kansas City, MO 64120-3510

Dear Sir:

This is in reference to your abbreviated new drug application dated October 20, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sucralfate Tablets USP, 1 g.

Reference is also made to your amendments dated August 14, 1995; March 27 and October 7, 1997; and January 22, March 12, and April 19, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sucralfate Tablets USP, 1 g, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Carafate® Tablets, 1 g of Blue Ridge Laboratories Inc.). Your disintegration testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74415

FINAL PRINTED LABELING

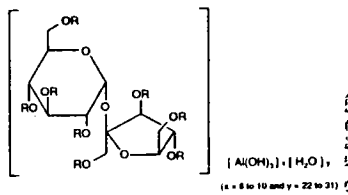
210035

SUCRALFATE TABLETS, USP

DESCRIPTION

Sucralfate is an α-D-glucopyranoside, b-D-fructofuranosyl-, octakis-(hydrogen sulfate), aluminum complex.

It has the following structural formula:



$[Al(OH)_3]_x \cdot [H_2O]_y$

(x = 8 to 10 and y = 22 to 31)

R = $SO_3Al(OH)_2$

Tablets for oral administration contain 1 g of sucralfate, USP.

Also contain: povidone, magnesium stearate, and colloidal silicon dioxide.

Therapeutic category: antiulcer.

CLINICAL PHARMACOLOGY

Sucralfate is only minimally absorbed from the gastrointestinal tract. The small amounts of the sulfated disaccharide that are absorbed are excreted primarily in the urine.

Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic, action. The following observations also appear pertinent:

1. Studies in human subjects and with animal models of ulcer disease have shown that sucralfate forms an ulcer-adherent complex with proteinaceous exudate of the ulcer site.
2. *In vitro*, a sucralfate-albumin film provides a barrier to diffusion of hydrogen ions.
3. In human subjects, sucralfate given in doses recommended for ulcer therapy inhibits pepsin activity in gastric juice by 32%.
4. *In vitro*, sucralfate absorbs bile salts.

These observations suggest that sucralfate's antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14 to 16 mEq of acid-neutralizing capacity per 1-g dose of sucralfate.

Clinical Trials

Acute Duodenal Ulcer

Over 600 patients have participated in well-controlled clinical trials worldwide. Multicenter trials conducted in the United States, both of them placebo-controlled studies with endoscopic evaluation at 2 and 4 weeks showed:

STUDY 1

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	37/105 (35.2%)	82/109 (75.2%)
Placebo	26/106 (24.5%)	68/107 (63.6%)

STUDY 2

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	8/24 (33%)	22/24 (92%)
Placebo	4/31 (13%)	18/31 (58%)

The sucralfate-placebo differences were statistically significant in both studies at 4 weeks but not at 2 weeks. The poorer result in the first study may have occurred because sucralfate was given 2 hours after meals and at bedtime rather than 1 hour before meals and at bedtime, the regimen used in international studies and in the second United States study. In addition, in the first study liquid antacid was utilized as needed, whereas in the second study antacid tablets were used.

Maintenance Therapy After Healing of Duodenal Ulcer

Two double-blind randomized placebo-controlled U.S. multicenter trials have demonstrated that sucralfate (1 g bid) is effective as maintenance therapy following healing of duodenal ulcers.

In one study, endoscopies were performed monthly for 4 months. Of the 254 patients who enrolled, 239 were analyzed in the intention-to-treat life table analysis presented below.

Duodenal Ulcer Recurrence Rate (%)					
		Months of Therapy			
Drug	n	1	2	3	4
Sucralfate	122	20*	30*	38†	42†
Placebo	117	33	46	55	63

*$P<0.05$, †$P<0.01$

In this study, prn antacids were not permitted.

In the other study, scheduled endoscopies were performed at 6 and 12 months, but for-cause endoscopies, were permitted as symptoms dictated. Median symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention-to-treat analysis for the 94 patients enrolled in the trial had the following results:

Duodenal Ulcer Recurrence Rate (%)			
Drug	n	6 months	12 months
Sucralfate	48	19*	27*
Placebo	46	54	65

*$P<0.002$

In this study, prn antacids were permitted.

Data from placebo-controlled studies longer than 1 year are not available.

INDICATIONS AND USAGE

Sucralfate tablets, USP are indicated in:

- Short-term treatment (up to 8 weeks) of active duodenal ulcer. While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the posthealing frequency or severity of duodenal ulceration.

Special Populations: Chronic Renal Failure and Dialysis Patients

When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum, such as aluminum-containing antacids, may increase the total body burden of aluminum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum-containing products adequately excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin plasma proteins. Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure.

Drug Interactions

Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses in the following: cimetidine, digoxin, fluoroquinolone, antibiotics, ketoconazole, l-thyroxine, phenytoin, quinidine, ranitidine, tetracycline, and theophylline. Subtherapeutic prothrombin times with concomitant warfarin and sucralfate therapy have been reported in spontaneous and published case reports. However, two clinical studies have demonstrated no change in either serum warfarin concentration or prothrombin time with the addition of sucralfate to chronic warfarin therapy.

The mechanism of these interactions appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. In all cases studied to date (cimetidine, ciprofloxacin, digoxin, norfloxacin, ofloxacin, and ranitidine) dosing the concomitant medication 2 hours before sucralfate eliminated the interaction. Because of the potential of sucralfate to alter the absorption of some drugs, Sucralfate should be administered separately from other drugs when alterations in bioavailability are felt to be critical. In these cases, patients should be monitored appropriately.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 g/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy

Teratogenic effects. Pregnancy Category B.
Teratogenicity studies have been performed in mice, rats and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2700 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system:

Gastrointestinal: diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth.

Dermatological: pruritus, rash

Nervous System: dizziness, insomnia, sleepiness, vertigo

Other: back pain, headache

Postmarketing reports of hypersensitivity reactions, including urticaria (hives), angioedema, respiratory difficulty, rhinitis, laryngospasm, and facial swelling have been reported in patients receiving sucralfate tablets. Similar events were reported with sucralfate suspension. However, a causal relationship has not been established.

Bezoars have been reported in patients treated with sucralfate. The majority of patients had underlying medical conditions that may predispose to bezoar formation (such as delayed gastric emptying) or were receiving concomitant enteral tube feedings.

Inadvertent injection of insoluble sucralfate and its insoluble excipients has led to fatal complications, including pulmonary and cerebral emboli. Sucralfate is not intended for intravenous administration.

OVERDOSAGE

Due to limited experience in humans with overdosage of sucralfate, no specific treatment recommendations can be given. Acute oral toxicity studies in animals, however, using doses up to 12 g/kg body weight, could not find a lethal dose. Sucralfate is only minimally absorbed from the gastrointestinal tract. Risks associated with acute overdosage should, therefore, be minimal. In rare reports describing sucralfate overdose, most patients remained asymptomatic. Those few reports where adverse events were described included symptoms of dyspepsia, abdominal pain, nausea, and vomiting.

DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer: The recommended adult oral dosage for duodenal ulcer is 1 g four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

Maintenance Therapy: The recommended adult oral dosage is 1 g twice a day.

HOW SUPPLIED

Sucralfate 1-g tablets, USP are supplied in bottles of 100 and 500. White, scored, oblong tablets embossed with "M" and "057".

Bottles of 100.....NDC 52555-057-01
Bottles of 500.....NDC 52555-057-05

Store at controlled room temperature 15° - 30°C (59° - 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
Merckle GmbH
Blaubeuren
Germany

For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Printed in USA Revised: Sept. 1997

USUAL DOSAGE: Read package insert for prescribing information.

201740

Store at controlled room temperature 15° - 30°C (59° - 86°F).

Pharmacist: Dispense in a tight, light-resistant container as defined in the USP.

WARNING: AS WITH ALL MEDICATIONS, KEEP OUT OF REACH OF CHILDREN

EACH TABLET CONTAINS:
sucralfate, USP.....1 gram

Sucralfate Tablets, USP 1 gram

CAUTION: Federal law prohibits dispensing without prescription

500 Tablets

MARTEC
PHARMACEUTICAL, INC.

NDC 52555-057-05

Manufactured by:
Merckle, GmbH.
Blaubeuren, Germany

For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No.:

Exp. Date:

201739

USUAL DOSAGE: Read package insert for prescribing information.
Store at controlled room temperature 15º - 30ºC (59º - 86ºF).
Pharmacist: Dispense in a tight, light-resistant container as defined in the USP.

WARNING: AS WITH ALL MEDICATIONS, KEEP OUT OF REACH OF CHILDREN

EACH TABLET CONTAINS:
sucralfate, USP...............................1 gram

MARTEC
PHARMACEUTICAL INC.

NDC 52555-057-01

Sucralfate Tablets, USP
1 gram

CAUTION: Federal law prohibits dispensing without prescription

100 Tablets

Manufactured by:
Merckle, GmbH.
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No.:

Exp. Date:

3 54328-057-01 8

201739

USUAL DOSAGE: Read package insert for prescribing information.
Store at controlled room temperature 15º - 30ºC (59º - 86ºF).
Pharmacist: Dispense in a tight, light-resistant container as defined in the USP.

WARNING: AS WITH ALL MEDICATIONS, KEEP OUT OF REACH OF CHILDREN

EACH TABLET CONTAINS:
sucralfate, USP...............................1 gram

MARTEC
PHARMACEUTICAL INC.

NDC 52555-057-01

Sucralfate Tablets, USP
1 gram

CAUTION: Federal law prohibits dispensing without prescription

100 Tablets

Manufactured by:
Merckle, GmbH.
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No.:

Exp. Date:

3 54328-057-01 8

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MARTEC
PHARMACEUTICAL INC.

NDC 52555-057-01

Sucralfate Tablets, USP
1 gram

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MARTEC
PHARMACEUTICAL INC.

NDC 52555-057-01

Sucralfate Tablets, USP
1 gram

CAUTION: Federal law prohibits dispensing without prescription

100 Tablets

Manufactured by:
Merckle, GmbH.
Blaubeuren, Germany
For:
Martec Pharmaceutical, Inc.
Kansas City, MO 64120

Lot No.:

Exp. Date:

3 54328-057-01 8

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74415

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 6

2. ANDA # 74-415

3. NAME AND ADDRESS OF APPLICANT
Martec Scientific, Inc.
U.S. agent for: ratiopharm GmbH & Co. Arzneimittel
Attention: Paul T. Sudhakar
1800 N. Topping
P.O. Box 33510
Kansas City, MO 64120-3510

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Sucralfate Tablets

9. AMENDMENTS AND OTHER DATES:

FIRM		FDA
Date of Submission	(10/20/93)	RF 11/9/93
Amendment	(12/02/93)	RF 12/17/93
Amendment	(01/20/94)	Filing 1/25/94
Amendment	(03/28/94)	NA LTR 3/10/98
Amendment	(06/02/97)	
Amendment	(10/07/97)	
Amendment	(01/22/98)	
Amendment	(03/12/98)	
Amendment	(04/19/98)	

10. PHARMACOLOGICAL CATEGORY
Anti-ulcerative

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
1 gram

15. CHEMICAL NAME AND STRUCTURE
$Al_8(OH)_{16}(C_{12}H_{14}O_{35}S_8)[Al(OH)_3]_x[H_2O]_y$ in which x= 8 to 10 and y = 22 to 31. Beta-D-fructofuranosyl, alpha-D-glucopyranoside, octakis (hydrogen sulfate), aluminum complex (USP Drug Substance); (USP Drug Product)

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 4/30/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74415

BIOEQUIVALENCE REVIEW(S)

Sucralfate Tablets, 1 gm
ANDA # 74-415
Reviewer: Hoainhon Nguyen
WP # 74415d.o93

Ratiopharm GMBH
Ulm, Germany
Submission Date:
October 20, 1993
March 27, 1997
(USAgent: Martec Pharm.)

Review of *In Vitro* (Disintegration) Data

In addition to the clinical study comparing the test product to the reference listed drug product, Marion Laboratories' Carafate® Tablets, 1 gm, the firm also conducted *in vitro* testing for the test and reference products. There is presently no USP or FDA-recommended dissolution testing required for the test product, but there is USP Disintegration testing specified for the product (USP 23, p. 1445).

The clinical data have been reviewed by the Division of Gastrointestinal and Coagulation Drug Products and the Division of Biometrics. The *in vitro* data are reviewed by the Division of Bioequivalence.

Disintegration Results: USP Specification: "NMT minutes in water at 37°C"

See the summary of the results attached to this review.

Comment:

1. The disintegration data for the test and reference products meet the USP specification, and therefore are acceptable.

2. The conclusion by the medical reviewer, Dr. Robert Prizont with the concurrence from Dr. Talarico, on the firm clinical study is summarized by Dr. Mary M. Fanning, Associate Director of Medical Affairs, OGD, as follows:

"...the generic sucralfate tablet formulation is equivalent to the marketed Carafate tablet in the short term treatment, up to 8 weeks, of active duodenal ulcer."

Recommendations:

1. The clinical study comparing Ratiopharm's generic sucralfate tablet formulation, 1 gm, with the marketed Carafate® tablet, 1 gm, by Marion Laboratories, has been found acceptable by the Division of Bioequivalence in consultation with the Division of Gastrointestinal and Coagulation Drug Products. The test product is deemed equivalent to the reference listed drug product for the short treatment of active duodenal ulcer, as specified in the INDICATION section of the marketed Carafate® label.

2. The *in vitro* disintegration testing of the test and reference product is acceptable.

The disintegration testing should be incorporated into the firm's manufacturing controls and stability program. The disintegration testing should be conducted water at 37°C. The test product should meet the USP specification of NMT minutes.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 2/27/98

Concur: _____ Date: 2/27/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-415 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/02-27-98/WP #74415d.o93
and X:\new\firmsnz\ratioph\ltrs&rev\74415bio.298

Attachment: 1 page (Summary of disintegration data)

CC: **ANDA 74-415**
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-652 /HNguyen

X:\NEW\FIRMSNZ\RATIOPH\LTRS&REV\74415BIO.298
Printed in final on / /98

Endorsements: (Final with Dates)
HFD-652/ H. Nguyen
HFD-652/ Y Huang 2/27/98
HFD-617/ L. Sanchez
HFD-65 / D. Conner 2/27/98

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 27-March 1997

1. **STUDY AMENDMENT** (STA) Strengths: 1 GM
Outcome: AC

2. **DISSOLUTION/DISINTEGRATION** (DIS) Strengths: 1 GM
Outcome: AC

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete
WINBIO COMMENTS:

WP# 74415d.093 Attachment 1 of 1

VI. BIOAVAILABILITY/BIOEQUIVALENCE [314.94(a)(7)]

H. CLINICAL SUPPLIES (continued)

3. In Vitro Dissolution Data

For this drug product, sucralfate tablets, the USP standards have not been issued; however, the proposed formulary has recommended the use of USP <701> DISINTEGRATION. No dissolution testing is required.

Disintegration testing was performed as part of the specifications for release of the product when the lot of sucralfate tablets to be used in this clinical study was manufactured. Additional disintegration data has also been obtained as part of the stability test program for the tablets packaged in containers and in unit dose packages. These data are given in the respective sections of the ANDA.

The reference product used in the clinical study, Carafate® brand of sucralfate tablets, was also subjected to disintegration testing.

The proposed specification for this drug product is: "Not more than ninutes in water at 37 degrees centigrade."

a. Test Product Disintegration Data (Lot No. 0259/A0)

DATE OF TEST	DESCRIPTION	RESULTS
03.28.90	Release testing from manufacturing	5 min
02.01.91	Start of stability program	5.17 min
08.14.91	6 month stability	2.87 min
02.19.92	12 month stability	2.00 min
02.10.93	24 month stability	3.25 min

b. Reference Product Disintegration Data (Lot No. K02590)

DATE OF TEST	DESCRIPTION	RESULTS
02.01.91	Start of stability program	1.08 min
08.14.91	6 month stability	0.83 min
02.19.92	12 month stability	1.33 min
02.10.93	24 month stability	3.15 min

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA: 74-415 SPONSOR : Ratiopharm GMBH
DRUG & DOSAGE FORM : Sucralfate Tablets, 1 gm

TYPE OF STUDY:	Clinical Study	
STUDY:	XAcceptable	□Not Applicable
DISINTEGRATION:	XAcceptable	□Not Applicable
WAIVER:	□Acceptable	XNot Applicable

REVIEWER: Hoainhon Nguyen
INITIAL:
BRANCH: I
DATE : 2/27/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D.
INITIAL :
BRANCH : I
DATE : 2/27/98

DIRECTOR: Dale Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL :
DATE : 2/27/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL :
DATE :

BIOEQUIVALENCY COMMENTS

ANDA: 74-415 APPLICANT: Ratiopharm GMBH

DRUG PRODUCT: Sucralfate Tablets, 1 GM

The Division of Bioequivalence has completed its review and has no further questions at this time.

The *in vitro* testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74415

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 74-415

FIRM: Martec Scientific, Inc.
U.S. agent for: ratiopharm GmbH & Co. Arzneimittel
1800 N. Topping
P.O. Box 33510
Kansas City, MO 64120-3510

DOSAGE FORM: Tablet STRENGTH: 1 g

DRUG: Sucralfate

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable as of 3/3/98.

BIO STUDY INFORMATION: The applicant performed in an in-vivo bioequivalence study to evaluate the subject drug product's clinical efficacy and safety compared to that of the reference drug product. Bio- acceptable as of 2/27/98.

METHODS VALIDATION: Not applicable; drug substance and drug product are compendial items.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

The stability of the drug product in the marketed containers stored at 30° C and 40° C/75% RH was investigated. In addition, the stability of the product while stored in the used for shipping was also studied. The data for lot 259/AO packaged in the market containers were within specification at room temperature conditions.

The company will perform the following stability tests:

TEST	SPECIFICATION	METHOD
Appearance	White, oblong tablet bisected and embossed with "M" and "057"	In-house

Identification Aluminum-detection Sucrose-octasulfate	positive	USP In-house
Content Uniformity		
Hardness		
Disintegration	NMT .min. for all of 6 tablets or all but 2 of 18	USP <701>
Acid Neutralization Eq		in-house
Content Uniformity		USP
Related Substances		In-house
Assay: Sucrose Octasulfate		In-house

LABELING: Acceptable as of 12/4/97.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH- The applicant manufactured a batch of tablets which was used for the clinical testing and stability testing of the drug product.

SIZE OF STABILITY BATCHES - The applicant has manufactured a new production batch (lot #2504-1-6 and lot #2504T6 according to the updated batch manfacturing record. A copy of the record along with data are found in Annex nos. 8 and 9 of the 6/2/97 amendment (p. 1897). The tablets were packaged in a new container closure configuration.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The company intends to one batch at a time to yield a production batch of

RECOMMENDATION: Approvable.

SIGNATURE: **DATE:**

cc: ANDA 74-415

Endorsements:
HFD-645/ALangowski/5/13/98 5/21
HFD-645/BTArnwine/5/15/98 5/22/98

x:\new\firmsam\martec\ltrs&rev\74415.apf
F/T by pah/5/20/98

APPROVAL - Summary

COMPONENT	MG/TABLET
Sucralfate	1000.00
Povidone, USP	
Magnesium Stearate, NF	
Colloidal Silicon Dioxide, NF	
Isopropyl Alcohol*, USP	
TOTAL	1065.3

*removed

The finished product specifications specified in the applicant's current version # F-S599-USA2.DOC

Test	Test mtd #	Specification
Description	in-house	
Weight Variation	in-house	
Uniformity of Dosage	USP <905>	
Tablet hardness	in-house	
Disintegration	USP <701>	
Moisture Content	Karl Fischer	

Identity: Aluminum-detection Sucrose-octasulfate	USP <191	
Assay (Sucrose-octasulfate)		
Acid Neutralization Equivalent	USP	
Related Substances	in-house	
Chromatographic Purity		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74415

CORRESPONDENCE

MARTEC
PHARMACEUTICAL, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

F.4

Fax amendment

To:	Mr. Doug Sporn, Director, OGD, FDA	**From:**	Paul T. Sudhakar (for ratiopharm GmbH)
ATTN:	Ms. Kassandra Sherrod, Project Manager	**Pages:**	26
Phone:	301-827-5847	**Date:**	04/19/98
Re:	**FACSIMILE AMENDMENT** TO ANDA 74-415, Sucralfate Tablets USP, 1 g	**CC:**	To: ANDA 74-415 Dr. Klaus Lichtenberger, M.D., ratiopharm

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Mr. Sporn:.

As stated in the FDA FACSIMILE deficiency cover letter of April 16, 1998, ratiopharm GmbH (via U.S. agent Martec Pharmaceutical, Inc.) is filing a FACSIMILE amendment to the above mentioned ANDA within the required 30 days.

The comments in the FACSIMLE deficiency letter are addressed in this amendment which is presented in one volume. Two hard copies of the entire amendment have been sent to OGD Document control room by FEDERAL EXPRESS.

Please contact me at (816) 241-4144 or at 800-822-6782, if you need additional information.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar
Authorized US agent for ratiopharm GmbH, Ulm, Germany
&
Executive Vice President, Martec Pharmaceutical, Inc.
Enclosures:

1. APPENDIX I – FDA Facsimile letter of April 16, 1998
2. APPENDIX II – Firm's Response to the Facsimile comments and attachments

MARTEC
PHARMACEUTICAL INC

FAX:800/287-7576
PHONE:800/822-6782

FACSIMILE AMENDMENT. ANDA 74-415.

FAX COVER SHEET

DATE: 4/19/98

TO: FDD OGD.

FAX NO: 301-827-4337

ATTENTION: Ms. Cassandra Sherrod Project Manager

FROM: PAUL T. Sudhar (agent for Patrapharm Gmbh

NO. OF PAGES: 27.

REMARKS:

Dear Ms. Sherrod.

Please find enclosed entire facsimile amendment to ANDA 74-415 Sucralfate tablets,

Please contact me at 1-800-822-6782, if all the pages do not come through.

Sincerely.

Paul T. Sudhakar

FACSIMILE AMENDMENT

APR 16 1998

ANDA 74-415

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Martec Pharmaceuticals U.S. Agent for ratiopharm GmbH & Co. PHONE: 816-241-4144

ATTN: Paul Sudhakar FAX: 816-483-5432

FROM: Kassandra Sherrod PROJECT MANAGER (301) 827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 20, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sucralfate Tablets USP, 1 g.

Reference is also made to your amendment dated March 12, 1998.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

CMC comments attached

X:\new\ogdadmin\macros\fxafax.frm

APR 16 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-415 **APPLICANT:** ratiopharm GmbH

DRUG PRODUCT: Sucralfate Tablets USP, 1g

The deficiencies presented below represent facsimile deficiencies.

Deficiencies:

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA 74-415 Applicant: ratiopharm GmbH

Drug Product: Sucralfate Tablets USP, 1g

The deficiencies presented below represent facsimile deficiencies:

Deficiencies & Responses:

MARTEC
SCIENTIFIC, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

(N/FA)

Fax amendment

To:	Mr. Doug Sporn, OGD, FDA	**From:**	Paul T. Sudhakar
ATTN:	Ms. Kassandra Sherrod, Project Manager	**Pages:**	46 47
Phone:	301-827-5847	**Date:**	03/12/98
Re:	FACSIMILE AMENDMENT TO ANDA 74-415, Sucralfate Tablets USP, 1 g	**CC:**	To: ANDA 74-415 Dr. Klaus Lichtenberger, M.D., ratiopharm

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Mr. Sporn:.

As stated in the FDA FACSIMILE deficiency cover letter of March 10, 1998, ratiopharm GmbH (via U.S. agent Martec Pharmaceutical, Inc.) is filing a FACSIMILE amendment to the above mentioned ANDA within the required 30 days.

All comments in the not approvable FACSIMLE are addressed in this amendment which is presented in one volume. Two hard copies of the entire amendment have been sent to OGD Document control room on 3/12/98 BY COURIER.

Please contact me at (816) 241-4144 or at 800-822-6782, if you need additional information.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar
Authorized US agent for ratiopharm GmbH, Ulm, Germany
&
Executive Vice President, Martec Pharmaceutical, Inc.
Enclosures:

1. APPENDIX I – FDA Facsimile not approvable letter of March 10, 1998
2. APPENDIX II – Firm's Response to the not approvable letter and attachments

MARTEC
PHARMACEUTICAL, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

FACSIMILE Amendment to ANDA 74-415

January 22, 1998

NEW CORRESP
NC

Mr. Doug Sporn
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – RM 278
7500 Standish Place
Rockville, MD 20855-2773

RE: FACSIMILE Amendment to ANDA 74-415 for Sucralfate Tablets USP, 1 g.

Dear Mr. Sporn:

In response to the facsimile deficiency letter of December 23, 1997 (presented as ***APPENDIX I***), and in accordance with 21 CFR 314.96, ratiopharm GmbH, herewith submits an amendment to the above-mentioned ANDA.

All comments of the not approvable letter are addressed in this amendment which is presented in one volume (***APPENDIX II***). Two copies of the entire amendment have been sent by courier to the Document Control Room for archival and review purpose.

Please contact me at (816) 241-4144 or at 800-822-6782, if you need additional information.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar

Authorized US agent to ratiopharm GmbH
Ulm, Germany
&
Executive Vice President
Martec Pharmaceutical, Inc.

RECEIVED
JAN 23 1998
GENERIC DRUGS

(816) 241-4144 CORPORATE OFFICE
800 822-6782 SALES & MARKETING
800 287-7576 FAX MACHINE

MARTEC
PHARMACEUTICAL, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

mtd
ps
10/14/97

MINOR Amendment to ANDA 74-415

October 7, 1997

Mr. Doug Sporn
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – RM 278
7500 Standish Place
Rockville, MD 20855-2773

RE: MINOR Amendment to ANDA 74-415 for Sucralfate Tablets USP, 1 g.

Dear Mr. Sporn:

In response to the not approvable letter of September 3, 1994 (presented as ***Attachment 1***), and in accordance with 21 CFR 314.96, ratiopharm GmbH, herewith submits an amendment to the above-mentioned ANDA.

All comments of the not approvable letter are addressed in this amendment which is presented in one volume. Two copies of the entire amendment are provided for archival and review purpose.

Please contact me at (816) 241-4144 or at 800-822-6782, if you need additional information.

Sincerely,

Paul T. Sudhakar.

Paul T. Sudhakar

Authorized US agent to ratiopharm GmbH
Ulm, Germany
&
Executive Vice President
Martec Pharmaceutical, Inc.

RECEIVED
OCT 0 8 1997
GENERIC DRUGS

(816) 241-4144 CORPORATE OFFICE
(800) 822-6782 SALES & MARKETING
(800) 287-7576 FAX MACHINE

MAR 10 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-415 **APPLICANT: ratiopharm GmbH**

DRUG PRODUCT: Sucralfate Tablets USP, 1g

The deficiencies presented below represent facsimile deficiencies.

Deficiencies:

Sincerely yours,

John D. Harrison 3/9/98

for Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: 74-415 APPLICANT: Ratiopharm GMBH

DRUG PRODUCT: Sucralfate Tablets, 1 GM

The Division of Bioequivalence has completed its review and has no further questions at this time.

The *in vitro* testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FACSIMILE AMENDMENT

MAR 10 1998

ANDA 74-415

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Martec Pharmaceuticals U.S. Agent for ratiopharm GmbH & Co. PHONE: 816-241-4144

ATTN: Paul Sudhakar FAX: 816-483-5432

FROM: Kassandra Sherrod PROJECT MANAGER (301) 827–5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 20, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sucralfate Tablets, [redacted].

Reference is also made to your amendment(s) dated January 22, 1998.

Attached are 3 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

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MARTEC
SCIENTIFIC, INC.

Amendment to ANDA 74-415

ORIG AMENDMENT
N/AC

June 2, 1997

Mr. Doug Sporn
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – RM 278
7500 Standish Place
Rockville, MD 20855-2773

RE: Amendment to ANDA 74-415 for Sucralfate Tablets USP, 1 g.

Dear Mr. Sporn:

In response to the not approvable letter of June 2, 1994, and in accordance with 21 CFR 314.96, ratiopharm GmbH, herewith submits an amendment to the above-mentioned ANDA.

All comments of the not approvable letter are addressed in this amendment which is presented in two volumes. Two copies of the entire amendment are provided for archival and review purpose.

Please contact me at (816) 241-4144 or at 1-800-822-6782, if you need additional information.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar

Authorized US agent to ratiopharm GmbH
Ulm, Germany
&
Executive Vice President
Martec Pharmaceutical, Inc.

RECEIVED
JUN 0 5 1996
GENERIC DRUGS

L.A.B. Inc.
700 Grand Avenue, Ridgefield, New Jersey 07657 • (201) 943-1180
FAX: 201-943-1144 • Telex: 469840 LAB ANL BIO CI (W.U.) • 4932378 LAB UI (ITT)

LAB

. . . worldwide pharmaceutical research

March 28, 1994

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs, HFD-632
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

1/AA

Re: ANDA 74-415

Dear Mr. Pollock:

This is an amendment to ANDA 74-415 Sucralfate Tablets, 1 gram, which was accepted for filing on January 25, 1994. The purpose of this amendment is to provide additional information regarding the stability of the tablets at room temperature. Included are the following:

1. Form 356: Form FDA 356h with an original signature by the applicant is herewith provided to indicate that the enclosed documents are an amendment to ANDA 74-415.
2. Stability Test Data: Stability test data for Lot 0259/AO sucralfate tablets stored at room temperature for 36 months are herewith provided. The tablets were packaged in bottles of 100 and 500 and in unit dose packages of 16.

LAB, Inc., the authorized United States Agent for the applicant, has relocated its facilities. For prompt resolution of questions pertaining to this application, please contact.

Robert B. MacArthur, Pharm.D.
Director of Clinical Research
LAB, Inc.
279 Lafayette Avenue
Cliffside Park, NJ 07010

Respectufully submitted,

Robert B. MacArthur, Pharm.D.
Director of Clinical Research

Enclosures

RECEIVED
MAR 31 1994
GENERIC DRUGS

ANDA 74-415

DEC 17 1993

L.A.B., Inc.
U.S. Agent for: ratiopharm GmbH & Co. Arzneimittel
Attention: Robert B. MacArthur, Pharm.D.
700 Grand Avenue
Ridgefield, NJ 07657

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Sucralfate Tablets, 1 g.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You are required to provide the manufacturer's certificate of analysis (COA) for the bulk drug substance, sucralfate [21 CFR 314.50(d)(1)(i)]. The manufacturer was identified in your application as

Thus, it will be not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Please provide a Form FDA 356h with an original signature with each amendment to your application.

Please provide an original signature with your debarment certification list of convictions [GDEA Section 306(k)(1) and (2)].

In order to comply with the regulations issued in the Federal Register (58 FR 47340-47352) issued September 8, 1993, you must provide a certification with an original signature in your abbreviated application that the field copy is a true copy of the technical section of the application described in 21 CFR 314.94 (a)(9) [21 CFR 314.94 (d)(5)]. In addition, the applicant shall submit a field copy of each amendment that refers to 21 CFR 314.94 (a)(9) [21 CFR 314.96].

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so , the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell, R.Ph.
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

for/ 12/16/93

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-415
cc: DUP /Jacket
DUP/Division File
HFD-82
HFD-File
Field copy
HFD-600/Reading File
HFD-615/MBennett

Endorsements: HFD-615/Gordon Johnston. Chief Revised 1st time 12/14/93 12/15/93 date
HFD-615/PRickman, CSC ____date 12/10/93
HFD-615/WRussell,CSO____ date
HFD-64[illegible]/Chem Branch Chief
WP File\B5:\ref.fil\74-[illegible] 12/16/93
F/T File hrw 12-10-93
ANDA Refuse to File!

L.A.B. Inc.
700 Grand Avenue, Ridgefield, New Jersey 07657 • (201) 943-1180
FAX: 201-943-1144 • Telex: 469840 LAB ANL BIO CI (W.U.) • 4932378 LAB UI (IT

LAB

...worldwide pharmaceutic... research

December 2, 1993

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs, HFD-632
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
DEC 0 6 1993
GENERIC DRUGS
NDA ORIG AMENDMENT

Dear Mr. Pollock,

This is in response to your letter of November 9, 1993 regarding ANDA 74-415, Sucralfate Tablets, 1 g. This application was submitted in good faith in accordance with FDA regulations and guidelines. Each of the items in question is discussed below by our regulatory group, in the order dictated by your letter.

1. Letter of Authorization for Drug Master File

2. Manufacturer's Certificate of Analysis for Drug Substance

A copy of the COA from the manufacturer for the bulk drug substance sucralfate was inadvertently omitted. Instead, the results of testing by a contract laboratory and provided by the agent for the manufacturer was included.

Did not provi...

3. English Translations for Manufacturer's Certificates of Analysis

The applicant, Merckle GmbH, does not rely upon the manufacturer's COA as a document for release if the vendor has not been qualified. Therefore, full compendial testing was performed by Merckle GmbH for the active substance and each excipient, and an English translation of the analytical test results was included in the application.

ORIGINAL

A copy of the COA, albeit in German, for each excipient was included to demonstrate the diligence of Merckle GmbH. The manufacturer's COA was not utilized to demonstrate the quality of the component/substance. Enclosed herewith are the English translations of the suppliers' COAs for the three excipients.

4. Draft Labeling

Only one copy of the package insert, rather than four copies, was included with the application. This was inadvertent omission and the additional copies for both the archival and review copies are herewith provided.

5. Signed Certification for Field Copy

A signed certification with an original signature was included with the Field Copy of the technical section.

Did not provide

6. Signed Certification Regarding Convictions

It was not understood that the statement regarding relevant convictions was required to be a signed certification, similar to that which was provided regarding debarment. The signature by the applicant on FDA Form 356h attests to the fact that all of the information contained within this ANDA is true and accurate.

Did not provide

The original signature on Form 356h was included in the Archival Copy.

Sincerely,

Robert B. MacArthur, Pharm.D.
Director of Clinical Research

Enclosures:
Package Insert (3 copies) - Pages 000031-000035
Translation of COA for Povidone - Page 001742A
Translation of COA for Magnesium Stearate - Page 001747A
Translation of COA for Colloidal Silicon Dioxide - Page 00152A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-415

NOV 9 1993

L.A.B. Inc.
U.S. Agent for: ratiophram GmbH & Co. Arzneimittel
Attention: Robert B. MacArthur, Pharm.D.
700 Grand Avenue
Ridgefield, NJ 07657

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Sucralfate Tablets, 1 g.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

2. You have failed to provide the manufacturer's certificate of analysis for the bulk drug substance, sucralfate.

3. You have failed to provide English translations for the provided manufacturer's certificates of analysis for the inactive ingredients (pp. 1742, 1747 and 1752).

Thus, it will not be filed as an abbreviated new drug application (ANDA) within the meaning of section 505(j) of the Act.

Please refer to the Office Director's letter to industry (copy enclosed) dated November 8, 1991 regarding the above requirements.

In addition, to be in compliance with 314.50(e)(2)(ii), you must provide four copies of the draft labeling with the application. You have provided one copy of the package insert. Please provide three additional copies for the archival copy. In the future please include four copies of the draft labels and labeling in both the archival and review copy.

Also, you must provide a signed certification with an original signature that the field copy is a true copy of the technical section contained in both the archival and review copies of the application [21 CFR 314.94 (d)(5)].

We note that you have provided a statement regarding relevant convictions on page 2373 of your application. However, this must be a signed certification with an original signature [GDEA Section 306(k)(1) and (2)].

Within 30 days of the date of this letter, you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell, R.Ph.
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Office Director's letter to industry

L.A.B. Inc.
700 Grand Avenue, Ridgefield, New Jersey 07657 • (201) 943-1180
FAX: 201-943-1144 • Telex: 469840 LAB ANL BIO CI (W.U.) • 4932378 LAB UI (ITT)

LAB

. . . worldwide pharmaceutica research

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs, HFD-632
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

January 20, 1994

RE: ANDA 74-415

Dear Mr. Pollock:

This is in response to your letter of December 17, 1993, regarding ANDA 74-415 Sucralfate Tablets, 1 g. This application was submitted in good faith in accordance with FDA regulations and guidelines. Each of the items in question is discussed below, in the order presented in your letter.

1. Manufacturer's Certificate of Analysis for Drug Substance

   A copy of the COA from the manufacturer for the bulk drug substance sucralfate was inadvertently omitted. The documentation supporting the manufacture of the sucralfate that was used in the biobatch is herewith provided as an amendment to the Chemistry and Manufacturing section of this application (Section XII.A.).

   Review of this submission will be facilitated if the amendment is read following page 001997. Three copies of this amendment are provided, for the Archival, Technical, and Field Copies of the ANDA.

2. Form FDA 356h

   A Form FDA 356h with an original signature is herewith provided to indicate that the enclosed documents are an amendment to ANDA 74-415.

3. Debarment Certification List of Convictions

   An original signature on the certification regarding debarment and convictions is herewith provided.